REMARKS

Status of the claims

Claims 21, 28, 40, 43, 99-104, 107-113, 120-135, and 137-143 were pending and claims 21, 28, 40, 99-104 and 107-108 were examined. Claims 28 and 40 have been amended as shown above to specify that the cells are isolated. As the Examiner has repeatedly indicated that such cells are fully enabled by the specification, it is clear that no new matter is raised as a result of these amendments, no new search required and the issues for appeal are simplified. Therefore, entry of the amendments after final is in order.

Applicants reiterate that rejoinder of the method claims is in order upon indication of allowable composition claims.

Rejections Withdrawn

Applicants note with appreciation withdrawal of the rejection of previous claims 21, 28, 40, 99-104, 107 and 108 under 35 U.S.C. § 112, 1st paragraph as allegedly failing to comply with the written description requirement. (Final Office Action, paragraph 3). In addition, the rejection of claims 21, 40, 99-102, 104, 107 and 108 under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the as-filed specification has also been withdrawn.

35 U.S.C. § 112, first paragraph, enablement

Previous claims 28, 40, 103, 107 and 108 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the as-filed specification on the grounds that only isolated cells are enabled. (Final Office Action, paragraphs 5-8).

Although Applicants submit that the previous claims were fully enabled throughout their scope, claims 28 and 40 have been amended to specify that the cell is isolated, thereby obviating the rejection.

35 U.S.C. § 103(a)

Claims 21, 28, 40, 99-104, and 106-108 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent Publication No. 20020107214 (hereinafter "Choulika") in

view of Bibikova et al. (2001) *Mol. Cell. Biol.* 21:289-297 (hereinafter "Bibikova") and further in view of Takeuchi et al. (2002) *Biochem. Biophys. Res. Commun.* 293:953-957 (hereinafter "Takeuchi") for the reasons of record. (Final Office Action, paragraphs 10-12).

Claims 21, 99-102 and 104

In response to Applicant's previous arguments that claims 21, 99-102 and 104 are non-obvious over the cited references because it was unpredictable as to whether a single vector carrying both the zinc finger nuclease and the donor sequence would actually work, the Final Office Action stated (Final Office Action, paragraph 12):

> While it may be that in some instances the use of two vectors as opposed to a single one would be advantageous, as indicated in the previous Office Action, one of skill in the art would be motivated to use a single vector for the benefit of delivering to the cell all the necessary components for recombination in a single vehicle. While it is agreed with Bibikova et al. teach that one could deliver chimeric nucleases along with a linear donor DNA molecule carrying the desired alteration (page 296, left column), Bibikova et al. do not teach that only a linear donor DNA could be delivered nor do they teach away from delivering donor DNA as part of the same vector encoding the chimeric nuclease or as circular DNA (e.g., another vector). In fact, Applicant has admitted that Choulika et al. teach delivering the repair substrate in a separate vector. As such, Choulika et al. teach that delivering donor DNA is not limited to linear DNA. Clearly, the art does not teach away from delivering donor DNA in other forms beyond linear DNA.

However, the standard for determining obviousness is not whether the references explicitly teach away from the claimed invention, but, rather, whether the cited references establish that the claimed invention is a predictable use of known prior art elements. As set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727; 82 USPQ2d 1385, 1397 (2007) and Patent Office Guidelines regarding determining obviousness issued in view of *KSR*, an obviousness rejection is only proper when the proposed combination of elements results in a predictable outcome (see, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007, emphasis added):

> The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one or ordinary skill in the art at the time of the invention.

The Supreme Court in *KSR* reiterated that an obviousness inquiry is fact-dependent and that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 82 UPSQ2d at 1389. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

Thus, a rejection cannot be predicated on the mere identification of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed subject matter, would have selected these components for combination in the manner.

In the instant case, all the claimed elements of claim 21 (and claims dependent therefrom) are not present in the cited references. Specifically, there is nothing in Choulika, Bibikova or Takeuchi that teaches a single vector that both encodes the nuclease and carries the donor nucleotide sequence. Given that all the elements of this claim are not set forth in the references, the obviousness rejection cannot stand on this basis alone.

Furthermore, there is no evidence whatsoever from the state of the art as a whole that the skilled artisan would have had any motivation to select a zinc finger nuclease and the donor nucleotide for placement on the same vector. The statement that it would somehow be a benefit to deliver all the necessary components for recombination is unsupported by any evidence except Applicants own specification (paragraph [0120] of the as-filed specification):

> In a preferred embodiment, the repair substrate and the chimeric nuclease can be introduced into the cell on a single vector. A single vector configuration may increase the efficiency for gene targeting.

It is improper to base an obviousness rejection on hindsight reconstruction using an applicant's specification as a guide. In this regard, the Supreme Court in *KSR* reaffirmed that the motivation to make the proposed modification cannot come from Applicants' own specification (*KSR,* 82 UPSQ2d at 1387, emphasis added):

> The teaching-suggestion-motivation test serves this purpose well. The test is flexible and allows judges and patent examiners to reject obvious inventions while protecting inventors from invalidation of their patent claims based on nothing more than the inventor's own disclosure of his invention. Absent the protection of the teaching-suggesting-motivation test, many truly inspired inventions are liable to be found obvious based solely on the disclosures contained in their own applications.

In the instant case, the assertion that providing cleavage and donor components on a single vector is not supported by any evidence in the references or state of the art and is therefore an improper basis of an obviousness rejection. In point of fact, Choulika and Bibikova clearly teach the use of separate nuclease expression cassettes and donor sequences. Takeuchi is similarly silent as to vector including sequences encoding both nuclease and donor substrate. Thus, the skilled artisan would want to keep the nucleases (which need to be transcribed into proteins in order to be functional) separate from an untranscribed donor nucleotide sequence. The art is similarly silent as to the claimed configuration. Without the teachings of the instant specification, the skilled artisan would have absolutely no expectation that the single nuclease/donor vector construction would be advantageous.

Simply put, there is no evidence that it was a predictable use of a single vector to deliver a sequence encoding a nuclease and a donor nucleotide sequence. To the contrary, the references teach explicitly that separate vectors (linear or circular) for the different components should be used.

In sum, there is no combination of Choulika, Bibikova, Takeuchi and the art as whole that shows that use of a single vector encoding a chimeric nuclease and carrying a repair substrate was a predictable, established use of these two separately used sequences. In the

absence of a showing regarding a predictable use of prior art elements, the obviousness rejection cannot be sustained.

Claims 28, 40, 103 and 106-108

Similarly, with respect to claims 28, 40, 103 and 106-108, the fact remains that there is absolutely not one shred of supporting evidence presented by the Examiner that the inserted "chromosomal" targets are not different from "endogenous chromosomal target sites." (Final Office Action, paragraph 12).

Indeed, the evidence of record establishes that cleavage of non-endogenous chromosomal targets is not at all predictive of cleavage of endogenous chromosomal targets as claimed. This evidence includes the teachings of the as-filed specification, which shows it was clearly not an established use of zinc finger nucleases to cleave endogenous chromosomal targets (see, paragraph [0160] of the as-filed specification, emphasis added):

> In the GFP gene targeting system the introduction of a DSB stimulated GT by >2000-fold and the absolute rate of gene targeting reached 3-5% when conditions were optimized. Such a system, however, depended on the prior introduction of a Sce site into the target gene and therefore **can not** be used for endogenous genes. To stimulate gene targeting at endogenous genes, a method to create sequence specific DSBs in those genes needs to be developed.

Simply put, a sequence inserted into a chromosome is not an endogenous target and it was certainly not considered predictable at the time of filing that zinc finger nucleases would cleave endogenous chromosomal targets.

The references themselves also teach that endogenous chromosomal targets are different than inserted chromosomal targets. Choulika is clear that the SceI binding site is not endogenous to a mammalian genome and thus must be inserted for cleavage to occur (see, Choulika, paragraph [0025], emphasis added):

> [0025] A model chromosomal loci was generated in which a site for the meganuclease I-SceI was introduced within the target region for recombination, and double stranded DNA cleavage via

> introduction of a vector encoding the restriction endonuclease was induced.

Still further evidence that Choulika's inserted cleavage site is entirely unlike an endogenous chromosomal cleavage site as claimed is found in Porteus et al. (2005) *Nature Biotechnology* 23:967-973 (Appendix A attached hereto). This paper, published well after Choulika, clearly indicates that endogenous chromosomal target sites for SceI are not readily found in mammalian genes (Porteus, Box 3 on page 969):

> Although several hundred different homing endonucleases with different recognition sites have been identified, the major limitation to using them in gene targeting is that most mammalian genes do not have recognition sites for them.

Thus, years after Choulika's priority date, the evidence establishes that inserted chromosomal targets were different than endogenous chromosomal targets. Accordingly, Choulika fails to teach or suggest cleavage of endogenous targets.

Furthermore, it remains the case that Choulika is not an enabling reference with respect to engineered zinc finger proteins and/or modified homing nucleases. It is well-established that in order to be available as a reference under 35 U.S.C. § 102/103, the reference must contain an enabling disclosure. *See, e.g., Chester v. Miller,* 906 F.2d at 1576 n.2, 15 USPQ2d at 1336 n.2 (Fed. Cir. 1990); *Titanium Metals Corp. of America v. Banner,* 778 F.2d at 781, 227 USPQ at 778 (Fed. Cir. 1985); *Scripps Clinic & Research Found. v. Genentech, Inc.,* 927 F.2d 1565, 1578, 18 USPQ2d 1001, 1011 (Fed. Cir. 1991); *Helifix Ltd. v. Blok-Lok Ltd.,* 208 F.3d 1339, 54 USPQ2d 1299 (Fed. Cir. 2000). In other words, the reference must "sufficiently describe the claimed invention to have placed the public in possession of it." See, *Minnesota Mining & Mfg. Co. ("3M") v. Johnson & Johnson Orthopaedics, Inc.,* 976 F.2d 1559, 1572, 24 USPQ2d 1321, 1332 (Fed. Cir. 1992); see also *In re Donohue,* 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985).

Choulika says nothing about designing or constructing zinc finger domains to bind a particular target sequence of choice. While Choulika mentions substituting "specific zinc finger binding domains" for the naturally occurring meganuclease DNA-binding domain of their

chimeric restriction enzymes in passing, there is absolutely nothing in this reference as to how to actually go about engineering a ZFP to bind to a selected, endogenous target site. See, paragraph [0025] of Choulika.

Not only does Choulika fail to describe how to engineer of ZFPs to bind to a selected target site, Applicants note that, as of Choulika's priority date (February 3, 1999), there were **no** publicly available references regarding engineering zinc finger binding domains that bound to endogenous chromosomal sequences. As such, Choulika does not enable production of engineered zinc finger proteins and, again, is silent as to endogenous chromosomal targets. Thus, this reference does not teach any of the elements of pending claims 28, 40, 103 and 106-108.

Likewise, Bibikova fails to teach cleavage of an endogenous chromosomal target. Instead, this reference specifically teaches that the target sequence for the naturally occurring ZFN is "microinjected" into oocytes (see, Bibikova, page 290, paragraph bridging left and right columns, emphasis added; see, also, Fig. 1(B) showing that target DNA is injected into oocytes):

> Here we characterize the cleavage abilities of the chimeric nuclease in *Xenopus laevis* oocytes. These enormous cells have a large capacity for homologous recombination that is readily accessed by <u>microinjection of appropriate substrates</u> ...

Therefore, Choulika and Bibikova are not cleaving endogenous chromosomal target, but rather non-endogenous substrates.

Nor is there any evidence supporting the contention that "the 'endogenous' limitation is at a minimum suggested by the references." (Final Office Action, paragraph 12). Choulika's failure to enable cleavage of an endogenous chromosomal target is detailed above. Similarly, the investigative team including Bibikova clearly chose <u>not</u> to cleave endogenous chromosomal DNA because they were unsure if zinc finger nucleases would result in targeting of endogenous chromosomal DNA by a repair substrate (rather than, for example, non-homologous end joining) (see, Bibikova page 296, right column, emphasis added):

> Several additional issues remain to be addressed to confirm the utility of chimeric nucleases as tools for gene targeting. Among these are demonstrating

discrimination against related sequences; proving the efficacy of zinc fingers designed to bind arbitrarily chosen sequences; and testing the cleavage of genuine **chromosomal** targets.

Furthermore, it is clear that Takeuchi's disclosure of Flp recombinase does not cure the deficiencies of Choulika and Bibikova regarding cells in which the repair substrate targets endogenous chromosomal DNA.

Thus, the cited references and state of the art do not demonstrate that it was a predictable, established use of zinc finger nucleases to cleave endogenous chromosomal targets, as required to support an obviousness rejection. Therefore, the rejection cannot stand.

CONCLUSION

Reconsideration of the application is requested in light of the foregoing amendments and remarks. If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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By: _____

Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicants

ROBINS & PASTERNAK LLP
1731 Embarcadero Road
Suite 230
Palo Alto, CA 94306
Tel. (650) 493-3400
Fax. (650) 493-3440